Rejection of Claim 37 Under 37 C.F.R. §1.75(c)

Claim 37 has been amended to overcome the Examiner's objection.

Rejection of Claims 18-36 Under 35 U.S.C. §112

The Examiner rejected claims 18-36, on the grounds that these claims contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to practice the invention. This rejection is respectfully traversed.

The Examiner asserts that the metes and bounds of "preventing or treating a disorder in a mammal" are unknown and that the specification provides no guidance on how to determine when a patient is in need of treatment with the peptides of the invention.

It is respectfully submitted that the specification describes how to obtain an antagonist of the function of a receptor which comprises an integral membrane protein having at least one transmembrane domain. It is clear to one skilled in the art that the highly specific antagonist peptides described in the specification are suitable agents for therapy of any disease in which it is known to be desirable to inhibit the function of a particular receptor.

The specification refers to many diseases which are known to be associated with overactivity of a particular receptor and in which, therefore, treatment with an antagonist of the function of that receptor would be desirable.

Applicants do not need to enable the identification of as yet unknown diseases and their therapy, but are providing an alternative, better, and more specific antagonist for diseases in which treatment with an antagonist of a particular receptor comprising an integral membrane protein with at least one transmembrane domain is indicated.

For example, the specification describes:

(1) That peptides selected in accordance with the invention may be used to treat disorders associated with specific receptor overactivity such as schizophrenia, which is associated with overactivity of the D2 dopamine receptor (page 12, lines 19-22); existing anti-psychotic

drugs have been shown to block the D2 receptor and therefore blockers or antagonists of the dopamine D2 receptor are the main candidates for neuroleptic drugs in the treatment of diseases such as schizophrenia, Huntington's Disease and Tourette's Syndrome (page 20, lines 15-19); such antagonists may also provide alternative treatments for substance abuse (page 20, lines 19-21);

(2) That adrenergic receptor antagonists are accepted therapeutic agents for treatment of hypertension, the adrenergic receptor and antagonist peptides of the invention providing new agents with previously unavailable specificity (page 23, lines 29-30);

(3) That the anti-asthmathic effects of theophyline and the anti-depressant and cognition-enhancing effects of caffeine are attributed to their action as adenosine receptor antagonists; adenosine receptor antagonists... are likely to be useful as anti-asthmatics, anti-depressants, anti-arrythmics, anti-Parkinsonian therapeutics, cognitive enhancers and renal protective agents (page 24, lines 25-30);

(4) That EGF receptors have been shown to act as oncogenes by mechanisms of overexpression or mutations that constitutively activate intrinsic tyrosine kinase activity of these proteins; the ability to inhibit or regulate the activity of these receptors by the peptides of the invention provides a new tool for the control of neoplastic growth in cancer (page 25, lines 25-34);

(5) That a number of drugs which have their effect on the brain act by binding to the GABA agonist site or receptor channel (i.e., will act as antagonists of the GABA receptor); these include benzodiazepines which are anxiolitic, and barbiturates which are anti-convulsant, (page 27, lines 17-21); and

(6) That the dopamine transporter and other monoamine transporters are the target of major classes of anti-depressant and psychostimulant drugs; one skilled in the art would realize that this indicates the effectiveness of dopamine transporter antagonists as anti-depressants and psychostimulants (page 28, lines 33-35).

The claims have been amended to more clearly indicate that they are directed to treatment of disorders for which administration of an antagonist of an integral membrane protein having at least one transmembrane domain is indicated. Accordingly, it is submitted that these claims are fully enabled by the specification as filed.

The Examiner comments, at page 4 of the Office Action, that based on the results reported for the β1-adrenergic-specific peptide, as reported at page 42, treatment of hypertension does not appear to work using these transmembrane peptide molecules (i.e., as it relates to claims 33 and 35). The Examiner should note that claims 33 and 35 are not directed to the β1-adrenergic receptor or its antagonist peptides but, rather, to the α1A-adrenergic receptor and its antagonist peptides.

With respect to the Examiner's objection to inclusion of the phrase "effective fragment or analogue thereof', this phrase does not appear in the amended claims. Support for the wording of the amended claims, for example amended claim 18, can be found in the specification as filed, at page 8, lines 20-24 which describes antagonist peptides comprising amino acid sequences corresponding to at least four consecutive amino acids of an integral membrane protein transmembrane domain, and at page 12, lines 22-23, which describes the invention as including peptides having one or more conservative amino acid substitutions.

Rejection of Claims 18-20, 27, and 36 Under 35 U.S.C. §112

Claims 18, 19, 20, 27 and 36 have been rejected as indefinite. The rejection has been rendered moot, in part, by the cancellation of claim 19 and the amendment of claim 20.

With respect to the Examiner's rejection of claims 18 and 36, it is believed that the meaning of these claims has been clarified by the enclosed amendments.

With respect to claim 18, the integral membrane protein has at least one transmembrane domain and the peptide comprises at least four consecutive amino acid residues from that transmembrane domain, or a variant thereof. With respect to claim 36, where the integral

membrane protein has several transmembrane domains, the peptide comprises at least four consecutive amino acid residues of any one of these transmembrane domains, or a variant thereof.

The Examiner's rejection of claim 27 probably was intended to be directed to claim 22. This rejection has been rendered moot by the amendment of claim 22.

Rejection of Claims 18-22 Under 35 U.S.C. §102

The Examiner has rejected claims 18-22 and 36 as anticipated by Lofts et al.

Lofts et al. studied the effect of intracellular expression of certain DNA sequences corresponding to portions of the *neu* oncogene as inhibitors of growth of *neu*-transformed cells *in vitro* and *in vivo*.

The DNA sequences expressed in the experiments described by Lofts et al. encoded not only the transmembrane domain of the tyrosine kinase encoded by the *neu* oncogene, but also portions of the extracellular and intracellular sequences of this kinase. The authors of the paper clearly thought these portions to be important, in that "the short extracellular and intracellular sequences would anchor the transmembrane portion in the correct orientation" (page 2814). Clearly, these authors thought it important that in order to interfere with the function of the tyrosine kinase, transmembrane sequences had to be expressed within the cell and inserted into the membrane in the correct orientation, by the normal intracellular process for insertion of this protein into the cell membrane.

They did not use peptides limited to the amino acid sequence of the transmembrane domain of the protein, nor did they administer transmembrane domain peptides to a mammal as a drug, as described by the present inventors.

Accordingly, claims 18-22 and 36 are not anticipated by Lofts et al., and in view of Lofts' belief in the importance of intracellular synthesis of the peptide sequence and insertion of the peptide into the cell membrane by the normal cellular process, this reference in no way suggests or renders obvious the claims of the present invention.

Rejection of Claims 18-24, 29 and 36 Under 35 U.S.C. §102(e)

Claims 18-24, 29 and 36 have been rejected as anticipated by Murphy et al. Murphy focuses on compounds which bind to G-protein coupled receptor ligands (GPR ligands). Murphy's work is based on the model described at column 2, lines 44-49, wherein "the binding of a GPR ligand to a G-protein coupled receptor involves multiple interactions between the functional groups on the GPR ligand and residues within the hydrophilic binding site of a receptor" and Murphy aims to interfere with this interaction by targeting the GPR ligand.

This is made clear in the objects of the Murphy invention, where it is indicated that an object of the invention is to provide polypeptides which bind GPR ligands or which may modulate GPR ligand binding to GPRs. And further "it is another object of the invention to provide synthetic or recombinant GPR polypeptides ... that can be used as potential modulators of G-protein coupled receptor function, by binding to GPR ligands or modulate GPR ligand binding, due to their expected biological properties ..." (column 6, lines 51-58).

The key to Murphy's approach is that the compounds of his invention should mimic the receptor and thereby attach to the ligand, preventing the natural receptor from binding to the natural ligand. This reference focuses on ligand-dependent peptides or peptides which act by their mimicry of natural receptors. In order to have their effect, such peptides must interact with the ligand.

At column 8, lines 33-37, the invention is described as relating to "G-protein coupled receptor (GPR) polypeptides which can be used to mimic naturally occurring or isolated GPRs, or ~~to modulate the binding of GPR ligands to GPRs~~, such as inhibition or enhancement of binding," i.e. of GPR ligands to GPRs.

Not all receptor activity, however, requires binding of a ligand to a receptor. For example, a number of disease states have been described in which membrane receptors have been found to be constitutively active, leading to a disease state. See, for example, the enclosed excerpt from *Encyclopedia of Human Biology*, 2nd. Edition, vol. 1 (1997), Academic Press, at Chapter 6 "Adrenergic and related G-protein coupled receptors".

In the last paragraph of this excerpt, at page 154, a couple of such examples are given, involving the LH receptor and the thyrotropin receptor. Use of a compound which targets the receptor ligand and binds to the receptor ligand will have no effect on such constitutive receptor activity.

In contrast, the present application focuses on the provision of antagonists of receptor function which act directly on the receptor itself, independently of the presence or absence of a receptor ligand.

The provision of antagonist peptides capable of antagonizing the function of integral membrane protein receptors enables the treatment of any disease state related to undesired receptor function, whether ligand stimulated or constitutive.

Accordingly, it is respectfully submitted that Murphy et al. does not anticipate claims 18 to 24, 29 and 36 of the present application.

SUMMARY

Claims 18-37 were pending in the application. Claim 19 is canceled, claims 18, 20, 21, 22 and 37 are amended, and new claims 60-65 are added. No new matter is introduced by the amendments.

Applicants request that the Examiner reconsider the application in light of the foregoing Amendment, and respectfully submit that the claims are in condition for allowance. If, in the Examiner's opinion, a telephonic interview would expedite the favorable prosecution of the present application, the undersigned attorney would welcome the opportunity to discuss any outstanding issues, and to work with the Examiner toward placing the application in condition for allowance.

Respectfully submitted,

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TABLE II
G Protein-Coupled Receptor-Linked Diseases in Humans

Receptor	Chromosome	Disease state	Type and function of mutation (loss (−) or gain (+) of function)
Rhodopsin	3q21	Retinitis pigmentosa	(−) apoptosis of rod cells
Rhodopsin	3q21	Stationary night blindness	(+) missense mutation
Blue opsin	7q22	Tritan color blindness (tritanopia)	(−)
Red opsin	X	Protan color blindness (protanopia)	(−) chromosome rearrangement
Green opsin	X	Deutan color blindness (deuteranopia)	(−) chromosome rearrangement
V_2 vasopressin	X	Nephrogenic diabetes insipidus type II	(−)
ACTH (MC2)	18p11.2	Isolated glucocorticoid deficiency	(−)
TSH	14q31	Hyperthyroidism	(+) missense; somatic mutation
LH	2p21	Familial precocious puberty	(+) missense; males only
		Leydig cell agenesis	
		Leydig cell hypoplasia	

mined. In other studies, internalized β_2AR were found in noncoated vesicles believed to be caveoli. The precise role played by these distinct populations of vesicles in the sequestration and down-regulation pathways is not clear at this time.

IV. G PROTEIN-COUPLED RECEPTORS IN DISEASE

Our present understanding of the structure–function relationships of the GPCR has advanced mainly because of the use of molecular biology techniques. Many investigators have shown by site-directed mutagenesis that substituting particular amino acid residues affects normal receptor function and sometimes even completely abolishes receptor function. These type of experiments raise the question of what happens if such mutations occur in nature? As mentioned earlier, GPCRs process a diversity of extracellular signals that are central to the regulation and maintenance of normal cell physiology, therefore it would be easy to envision how aberrant functioning GPCRs may underlie a variety of disease states. Indeed, a number of acquired or hereditary human diseases such as certain types of blindness, diabetes insipidus, hyperthyroidism, and neoplasia have been linked to defective GPCRs (see Tables II and III).

TABLE III
G Protein-Coupled Receptors Associated with Human Diseases

Receptor	Disease state
Adrenergic	Malignant hypertension
Angiotensin AT2	Hypertension
Dopamine	Schizophrenia, alcoholism
Endothelin ET_B	Hirschsprung disease type II
5-HT (serotonin)	Anxiety, depression, migraine
Tachykinin	Bronchial asthma
Thromboxane	Impaired platelet aggregation (bleeding disorder)

The mechanisms by which abnormalities in G protein-mediated signal transduction cause disease are diverse and are not limited to abnormal GPCRs alone. Defects in other molecules involved in the signal transduction pathway of GPCRs, such as the endogenous ligands, G proteins, and effector molecules, have also been linked to human diseases. However, this review focuses only on disease states associated directly with GPCRs. In theory, diseases could result from genetic defects in GPCRs that lead to constitutively active receptors resulting in increased signal transduction. On the other hand, mutations may lead to a variety of defective receptor functions, including synthesis and membrane targeting, ligand binding, G protein coupling, or phosphorylation resulting in decreased signal transduction. The clinical manifestation of these defects would depend on the severity of the receptor dysfunction and on the cellular distribution and normal function of the receptor. If the receptor is widely expressed and its function is ubiquitous to many tissue types, then mutations may be lethal. However, if the receptor is expressed in highly specific